REMARKS

Applicant intends this response to be a complete response to the Examiner's **14 June 2005** Non-Final Office Action. Applicant has labeled the paragraphs in his response to correspond to the paragraph labeling in the Office Action for the convenience of the Examiner.

Election/Restrictions

1. Applicant acknowledges that the election/restriction requirement is now made final. However, Applicant's attorney is still very concerned with the scope of the restriction practice now plaguing practitioners before the USPTO. Before the change in law to the 20 year from the date of filing patent term, divisional practice was not detrimental to the patentee, and with that change the practitioners believed that over reaching election/restriction practice would be less used. However, the USPTO is now routinely restricting cases even when there is a common features in the claims. This practice is requiring considerable more financial strain on all client and is very counterproductive to handling the case load before the Office. I would greatly appreciate you mentioning to your committee that restriction practice guidelines need to be revisited.

Claim Rejections - 35 USC § 102/103

4. **Claims 7, 8, 10-13, 15, 21-29, 31-40, 42-47** stand rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kao et al. (6,399,335 B1).

The Examiner contends as follows:

> Kao et al. provides methods and compositions for polymerizing a particular nucleotide with a polymerase. In general, the method involves (a) forming a mixture of a polymerase and a nucleoside triphosphate (NTP) comprising α, β and γ phosphates and a γ-phosphate phosphoester-linked functional group; and (b) incubating the mixture under conditions wherein the polymerase catalyzes cleavage of the NTP between the α and β phosphates, liberating a pyrophosphate comprising the functional group and polymerizing the resultant nucleoside monophosphate. i.e. incorporates the nucleoside monophosphate in a nascent polynucleotide. Col. 2-4.
>
> A variety of functional groups compatible with the polymerization reaction are provided. In one embodiment, the functional group is a detectable label and the method further comprises the step of detecting the label, wherein a wide variety of chromogenic and luminogenic labels are provided.
>
> In another embodiment, the functional group is a cell delivery enhancing moiety, --OR, wherein R is independently selected from: substituted or unsubstituted, (C1-C18) alkyl, alkenyl, alkynyl and aryl, each inclusive of carbocyclic and heterocyclic. These substituents provide enhanced therapeutic availability through

enhanced gut or blood stability, cellular and/or membrane permeability, host phosphatase stability, etc. This aspect provides a wide variety of generally membrane permeable, relatively hydrophobic R substituents.

The invention provides kits for assaying polymerase reactions in standard laboratory spectrophotometers. The kits are designed so that the researcher can replace one or more components with the sample they wish to test.

Col. 4 shows exemplary of detectable label (Table 1A (4-aminophenol for example) and labeled NTP's (Table 1B). see also col. 7-12 . Which are viewed to be inclusive of the instant claims 23-26 for example.

Applicants claims are directly to a method for altering base incorporation fidelity using tagged dNTPs or tagged ddNTPs. Although Kao et al discloses sequencing reactions using tagged dNTPs, Kao et al or any other reference disclosed that the tagged or labeled nucleotides would increase polymerase base incorporation fidelity. The discovery allows simple modified nucleotides to be used sequencing reactions to decrease the number of incorrect reading and mismatches and thereby reducing error rates and increasing sequencing read confidences. Kao et al does not disclose the use of such modified nucleotides to alter polymerase extension fidelities relative to the unmodified nucleotides.

Because Kao et al does not disclose the use of modified nucleotides to alter base incorporation fidelity, Kao et al cannot anticipate this invention. Applicants, therefore, respectively request withdrawal of this rejection.

5. **Claims 7, 8, 10-13, 15, 21-24, 27-29, 31-33,36-40, 42-44, 47** stand rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Williams (WO 00/36151).

The Examiner contends as follows:

Williams et al. provide assay methods for the detection of pyrophosphate cleavage, which is advantageous in number of biological reactions. For example, in DNA polymerase reaction (pages 7-8). William et al. discloses a method comprising the step of adding a modified nucleotide having a γ-phosphate with a fluorophore moiety attached thereto (pages 4-5, 16). Said method comprising a nucleotide polymerizing agent (polymerase). Further page 19 discloses that there are many linking moieties and methodologies for attaching fluorophore to nucleotides. Figure 4 shows the preferred linkers, which is viewed to be inclusive of instant claim 24. Additionally page 21 shows that the linker can comprised aryl groups (line 13). Suitable fluorophore include EDANS, (page 17, last paragraph). Page 7 shows that suitable NTPs include ATP. Williams et al. provides kits and integrated for practicing the assays (page 5). The polymerase is a DNA polymerase such as DNA polymerase I, II, or III, for example (page 8).

Claims 7, 13, 15, have added functions which the prior arts have not analyzed (base incorporation fidelity); but given the above 102 rejections analysis substantiating the basic characterization of the composition of the invention being the same as the references, these added characteristics are presumed to be inherent in the prior arts compositions.

As it is pointed in In re Fitzgerald (205 USPQ), page 594, 2nd col., 1st full paragraph, supports the shifting of the burden of proof to the applicant that the instantly claimed invention is novel and unobvious over the prior art. Since' both the prior arts and the instant application prepare and use composition which appeared to be identical, the prior arts therefore suggest that the composition therein disclosed are effective in assay suggesting the instant application under 35 U.S.C. § 103(a).

Applicants claims are directly to a method for altering base incorporation fidelity using tagged dNTPs or tagged ddNTPs. Although Williams et al discloses sequencing reactions using tagged dNTPs, Williams et al or any other reference disclosed that the tagged or labeled nucleotides would increase polymerase base incorporation fidelity. The discovery allows simple modified nucleotides to be used sequencing reactions to decrease the number of incorrect reading and mismatches and thereby reducing error rates and increasing sequencing read confidences. Williams et al does not disclose the use of such modified nucleotides to alter polymerase extension fidelities relative to the unmodified nucleotides.

Because Williams et al does not disclose the use of modified nucleotides to alter base incorporation fidelity, Williams et al cannot anticipate this invention. Applicants, therefore, respectively request withdrawal of this rejection.

The Commissioner is authorized to charge the additional claim charges to Deposit Account No. 501518. The Commissioner is also authorized to charge any underpayment or credit any overpayment to Deposit Account No. 501518.

If you have any questions, please call me at 713.977.7000.

Respectfully Submitted,

Date: **November 14, 2005**

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